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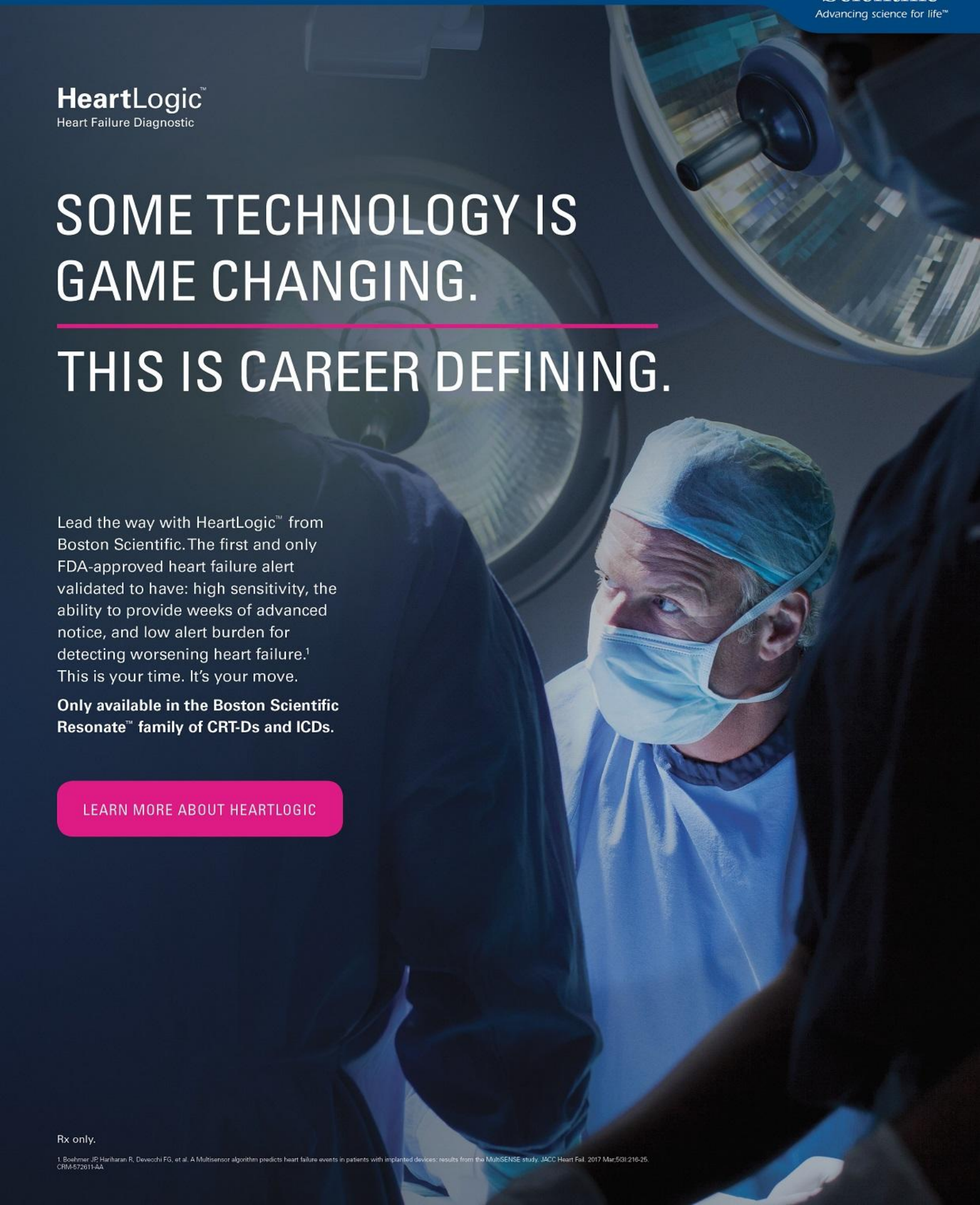

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Non-Invasively Quantified Changes in Left Ventricular Activation Predict Outcomes in Patients Undergoing Cardiac Resynchronization Therapy

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Background: Changes in left ventricular (LV) activation after cardiac resynchronization therapy (CRT) influence survival but are difficult to quantify non-invasively.

Methods and Results: We studied 527 CRT patients to assess whether non-invasive quantification of changes in LV activation, defined by change (Δ) in QRS area(QRSA), can predict outcomes after CRT. The study outcome was time until LV assist device(LVAD), cardiac transplant, or death. The 3-dimensional QRSA was measured from clinical 12 lead ECGs which were transformed into vectorcardiograms using the Kors method. QRSA was calculated as $(QRSx^2+QRSy^2+QRSz^2)^{1/2}$; ΔQRSA was calculated as post-QRSA minus pre-QRSA, where a negative value represents a reduction in LV activation delay. Kaplan Meier plots and multivariable Cox proportional hazards models were used to relate ΔQRSA area with outcomes after stratifying the population into quartiles of ΔQRSA. The median baseline QRSA of 93.6μVs decreased to 59.7μVs after CRT. Progressive reductions in QRSA with CRT were associated with a lower rate of LVAD, transplant, or death across patient quartiles($p<0.001$). In Cox regression analyses, ΔQRSA was associated with outcomes independent of QRS morphology and other clinical variables [Q1(greatest decrease) vs. Q4(smallest change = reference), HR 0.45, CI 0.30-0.70, $p<0.001$]. There was no interaction between ΔQRSA and QRS morphology.

Conclusions: CRT induced ΔQRSA was associated with clinically meaningful changes in event free survival. ΔQRSA may be a novel target to guide lead implantation and device optimization.

Key words: cardiac resynchronization therapy, vectorcardiography, dyssynchrony, electrocardiography, outcomes, heart failure

Introduction

Cardiac resynchronization therapy (CRT) is a well-established therapy for patients with systolic heart failure and evidence of electrical dyssynchrony on the 12-lead ECG. Successful electrical resynchronization reduces overall left ventricular (LV) activation delays and is associated with improvements in LV structure and function,[1,2] affording improvements in heart failure, quality of life, and survival. Although the importance of CRT induced improvements in LV activation are well recognized, these changes are difficult to quantify rapidly and non-invasively. Prior studies show that the change in QRS duration after CRT pacing is inconsistently associated with likelihood of CRT benefit.[3,4]

Recently published work from our group[5] and others[6-8] suggests that 12-lead ECG derived vectorcardiographic (VCG) representations of ventricular activation may be useful for identifying an electrical substrate amendable to CRT. In these studies, a larger VCG derived QRS area (QRSA) on the baseline ECG was associated with increased likelihood of CRT response[7] and more favorable long-term outcomes[5,8] independent of QRS duration and morphology. These findings strongly suggest that QRSA is a robust non-invasive measure of LV activation delay. Based on these findings we sought to determine if non-invasive quantification of changes in LV activation, defined by absolute change in QRSA (ΔQRSA), could predict outcomes after CRT. We hypothesized that CRT induced reductions in QRSA would be associated with improved long-term outcomes.

Methods

Study population

We performed a retrospective analysis of patients who received a *de novo* CRT with defibrillator from April 2006 – September 2015 at Duke University Hospital. LV lead targeting was generally performed using an anatomic approach, guided rby occlusive coronary sinus venography, with the goal to implant in a lateral branch and maximize distance from the RV lead. For patients with quadripolar leads, we selected the electrode pair with maximal electrical delay that had an acceptable capture threshold without phrenic nerve stimulation. Echocardiographic optimization was performed rarely, usually in the setting of CRT non-response. Patients were first identified using an institutional dataset prepared for submission to the National Cardiovascular Data Registry. For this study, patients were required to have an LV ejection fraction (LVEF) of ≤35%, a QRS ≥120ms, and a digital ECG at baseline (≤180 days prior to CRT implantation) and ≤ 90 days after the index procedure. Patients were excluded if they died prior to discharge or if a follow-up ECG did not demonstrate evidence of CRT pacing. If multiple ECGs were available in the allowable pre- and/or post-CRT time frame we utilized the ECG closest to the procedure date. The study was approved by the Duke Institutional Review Board.

ECG and VCG Analyses

Clinically obtained ECGs were reanalyzed in the GE MUSE Cardiology Information System version 8.0.2.10132 with analysis software version 241 (GE Healthcare, Chicago, IL, USA) and exported in XML format. QRS morphology was designated by two readers (DF and KE) blinded to outcome. Left bundle branch block (LBBB) morphology was

further divided into strict and non-strict LBBB using the Strauss criteria.[9] Notably, the Strauss criteria incorporate information on both QRS duration and characteristics (e.g. notching). QRS onset and offset and thereby QRS duration as detected by the software were over read and manually corrected if needed.

VCGs were derived from the XML files using customized MATLAB software (MathWorks, Inc., Natick, MA, USA) using the Kors matrices[10] based on previous data[5] suggesting VCGs resulting from the Kors transformation were more predictive of outcomes after CRT compared to Inverse Dower transformed VCGs.[11] We calculated the QRSA[5,7] for each pre- and post- CRT ECG using the median complex. The area under the depolarization curve was calculated for each of the 3 planes (X,Y,Z). The 3-dimensional QRSA was calculated as $(QRSx^2 + QRSy^2 + QRSz^2)^{1/2}$. The absolute CRT induced change in QRS area (ΔQRSA) was calculated as post-CRT QRSA minus pre-CRT QRSA; with this convention, a negative value represents a reduction in LV activation time which we hypothesized would represent a favorable prognostic sign. In contrast, a $\Delta QRSA > 0$ (i.e. a positive value) would represent an overall increase in LV activation time which we hypothesized would identify increased risk for adverse outcomes.

End Points

The study endpoint was incident left ventricular assist device (LVAD), cardiac transplant, or death. End point occurrence was determined via a May 24, 2017 query of the Duke Enterprise Data Unified Content Explorer, which incorporates data from billing claims, hospital records, and the Social Security Death Index.[12]

Statistical Analyses

Baseline characteristics of the overall study population and after stratification by quartile of ΔQRSA were described using proportions for categorical variables and medians and interquartile ranges for continuous variables. The 1st ΔQRSA quartile was defined as the quartile with the most negative ΔQRSA (greatest decrease in QRSA with CRT), the 4th ΔQRSA quartile was defined as the quartile with the most positive ΔQRSA (smallest decrease or increase in QRSA with CRT), and the 2nd and 3rd quartiles represented intermediate groups. Differences between groups were tested using the Chi-square test for categorical variables and Kruskal Wallis Rank Sum test for continuous variables. Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[13]

The unadjusted long term association between ΔQRSA quartile and time until transplant, LVAD, or death, was visually depicted using a Kaplan Meier plot and differences were assessed using the Log Rank test. The adjusted association between ΔQRSA quartile and time until transplant, LVAD, or death, was assessed using Cox proportional hazards models with Q4 as the reference group. Schoenfeld Residual plots were created to confirm no violation of the proportional hazards assumption. Adjustment variables included age, sex, atrial fibrillation or flutter, ischemic heart disease, ejection fraction, QRS morphology, beta blocker use, ACEi or ARB use, diabetes, NYHA class, and reduced eGFR, defined as <60 mL/min/1.73m^2. We assessed for interactions between model variables prior to inclusion in Cox regression analyses. The association between ΔQRSA (across the continuous range) and outcomes was assessed using an adjusted restricted cubic spline with 3 knots with a ΔQRSA of 0 being assigned a hazard ratio of 1. Several subgroup analyses were performed handling ΔQRSA as a continuous variable in unadjusted cox regression analyses. Statistical analysis was performed in RStudio

version 1.1447 (RStudio, Inc, Boston, MA, USA) running R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). A $p<0.05$ was considered statistically significant for all analyses except for during interaction testing where a prior decision was made to use $p<0.01$ to account for multiple testing.

Results

A total of 1001 patients underwent CRT-D implant during the study period. After excluding patients with missing ECG (n= 407), QRS duration <120ms (n=39), LVEF>35% (n=18), death prior to discharge (n=7), non-CRT paced QRS morphology on the follow-up ECG (n=1),or poor quality follow-up ECG (n=2), a total of 527 patients were available for analysis. The overall study population was older (67.7 years, IQR 57.6-75.2), predominantly male (69.4%), and demonstrated a severely reduced ejection fraction (25.0%, IQR 20.0-30.0) with advanced HF symptoms (81.2% NYHA III symptom class). Medical comorbidities were common, including ischemic cardiomyopathy (54.1%), hypertension (71.5%), diabetes (38.3%), and atrial fibrillation or flutter (34.2%). LBBB was present in 64.2% of patients and the median QRS duration was 160 ms (IQR 144-180). Baseline clinical and electrocardiographic characteristics are depicted in **Tables 1 and 2**, respectively.

The median baseline QRSA of the overall population was 93.6µVs (IQR 61.3-127.3) and this decreased to 59.7µVs (IQR 41.7-82.8) with CRT pacing ($p<0.0001$)(**Figure 1**). After the overall population was stratified by quartile of ΔQRSA, the heterogeneity in ΔQRSA across the population became evident (**Figure 1**). Patients with the most negative ΔQRSA (largest reduction in LV activation delay) were more commonly female, had

non-ischemic cardiomyopathy, a longer baseline QRS duration, LBBB or RV paced ECG, and demonstrated a larger baseline QRSA. Patients with a smaller reduction (or even increase) in QRSA with CRT more commonly had RBBB, atrial fibrillation or flutter, chronic lung disease, a prior ICD, or treatment with amiodarone. Baseline clinical and electrocardiographic characteristics by ΔQRSA quartile are depicted in **Tables 1 and 2**, respectively.

CRT delivery strategies are depicted in **Table 3**. Median paced AV delay was 130ms (IQR 130-170ms) and median sensed AV delay was 100ms (IQR 100-120ms); AV delays did not vary by ΔQRSA quartile (p=0.62 and p=0.78, respectively). VV offset programing was variable and devices were most commonly programmed to deliver simultaneous biventricular stimulation. AdaptiveCRT was programmed on in 10.8% of patients and was somewhat more common among patients in Q1 (overall p=0.07). Quadriploar leads were implanted in 15% of patients and the proportion did not vary by ΔQRSA quartile (p=0.15). of note, quadripolar leads and AdaptiveCRT programming were not clinically available until later in the study period.

The median follow-up time was 1137 (interquartile range: 621-2004) days. Of the 247 patients who met the primary endpoint, 17 underwent LVAD implantation, 24 underwent heart transplantation, and 206 died. ΔQRSA (by quartile) was strongly associated with incident LVAD, transplant, or death in an unadjusted Log Rank analysis (p<0.001, **Figure 2**). Examination of the Kaplan Meier curve demonstrates that greater reductions in QRSA were associated with increasingly favorable long term outcomes across study quartiles. An adjusted Cox proportional hazards model (with Q4 as the reference group) demonstrated that ΔQRSA was significantly associated with outcomes (**Figure 3**);

although the point estimate suggested that Q1, Q2, and Q3, all had more favorable outcomes compared to Q4, the only difference reaching statistical significance was the Q1 vs. Q4 comparison. Results were similar with adjustment for amiodarone use, which was most common in Q4. There were no statistical interactions between baseline QRS morphology, ΔQRSA, and outcome. An adjusted spline analysis (**Figure 4**) demonstrated that the relationship between ΔQRSA and incident LVAD, transplant, or death was preserved across the continuous range.

LBBB

The LBBB cohort (n=338) was subsequently divided into ΔQRSA quartiles (similar to the approach for overall population) for subgroup analyses. Compared to Q4 patients (those with the smallest decrease or an increase in QRSA with CRT), Q1 (adjusted HR 0.39, CI 0.23-0.65) and Q2 (adjusted HR 0.55, CI 0.34-0.89) patients were significantly less likely to experience transplant, LVAD, or death (**Figure 5**).

Subgroup analyses

Additional subgroup analyses were performed handling ΔQRSA as a continuous variable (**Table 4**). In these analyses, ΔQRSA demonstrated predictive value regardless of age, sex, PR interval, QRS duration or history of coronary artery disease. ΔQRSA demonstrated predictive value among LBBB (but not non-LBBB or RV paced) patients, those with a higher ejection fraction (≥20%), and those with a greater baseline QRSA. ΔQRSA significantly predicted outcomes among patients with no atrial arrhythmias; the association among patients with atrial arrhythmias demonstrated borderline significance (p=0.052).

Discussion

This study, which related non-invasively assessed CRT induced changes in LV activation to clinical outcomes, has several relevant findings. First, although the overall study population demonstrated reductions in QRSA (consistent with CRT induced improvements in LV activation), significant variability existed across the population, and a significant minority of the overall population demonstrated worsened LV activation with CRT. Second, greater reductions in QRSA were associated with female sex, LBBB, longer baseline QRS duration, larger baseline QRS area, non-ischemic cardiomyopathy, and absence of atrial arrhythmias or lung disease. Third, CRT-induced reductions in QRSA were associated with clinically meaningful differences in event free survival. Finally, the relationship between ΔQRSA and outcomes was preserved across the continuous range and no clinically relevant threshold could be identified. These study findings have important implications for our overall understanding of the impact of CRT on LV activation and suggest that ΔQRSA is a novel and powerful predictor of CRT outcomes that could have the potential to improve LV lead implantation and device optimization algorithms.

Our understanding of the importance of the electrical substrate on outcomes after CRT has improved over the past two decades.[14] Early landmark CRT trials enrolled patients with QRS prolongation regardless of QRS morphology based on the general assumption that patients with QRS prolongation had at least some amount of left ventricular activation delay.[15-18] Subsequent analyses demonstrating patients with LBBB were more likely to benefit from CRT[3,19] (presumed due to greater extent of LV activation delay)[20] have underscored the importance of the electrical substrate. However, a significant

minority of LBBB patients do not respond to CRT[19,21] and an important minority of non-LBBB patients do appear to benefit from CRT[22,23] although this remains controversial. Furthermore, it is increasingly recognized that optimal LV lead position[24-26] and device programming algorithms[27] affect CRT outcomes as they directly impact the activation wavefronts responsible for LV depolarization. Although prior work[1,2] has compared baseline and paced ECG activation patterns to predict CRT response in LBBB patients, it has relied on complex, labor intensive scoring systems which may be challenging to integrate into a busy clinical practice.

ΔQRSA represents a powerful summative parameter than incorporates information on the complex interaction between the baseline electrical substrate and the CRT induced activation wavefronts. Although patients with the greatest reduction in QRSA (i.e. most negative ΔQRSA) commonly had a LBBB, the association between ΔQRSA and outcomes was statistically independent of QRS morphology (as well as sex, cardiomyopathy etiology, and other characteristics commonly associated with CRT response). Furthermore, the magnitude of the association between ΔQRSA and outcomes was *greater* among the LBBB patients (compared to the overall cohort). These findings confirm that ΔQRSA is much more than a proxy for QRS morphology, but rather a powerful measure of the *effectiveness* of resynchronization and novel predictor of CRT response.

Several studies have demonstrated that clinical outcomes are improved when the LV lead is implanted in a location with delayed electrical activation, compared to either QRS onset[24,25,28-30] or the sensed signal on the RV lead.[31] Importantly, emerging evidence has suggested that (1) an optimal electrical location does not always correspond to the

anatomic segments that are most commonly associated with CRT response and (2) assessment of electrical delay may improve outcomes among patients at high risk for CRT non-response.[30]

Despite the mounting data and compelling physiologic rational for incorporating electrical delay into a care strategy, there are several limitations to this strategy. Due to the anisotropic nature of wavefront propagation in ventricular myocardium (which often has regions of functional block), it cannot be assumed that the site of latest activation (delayed conduction *to* a site) necessarily represents the best site for LV pacing (where a wavefront is propagating *away* from a site). Thus, electrical delay is an *indirect* measure of the potential for resynchronization with pacing from a given site. Furthermore, use of electrical location alone to guide lead implantation and programming would leave the electrophysiologist unable to understand the potential benefit of using LV only pacing relative to biventricular pacing, V-V offset, and multipoint pacing. Importantly, ΔQRSA is a quantitative, continuous measure that *directly* measures the quality of resynchronization. Further studies are required to compare ΔQRSA relative to LV electrical delay and determine if a ΔQRSA guided approach can result in improved patient outcomes.

Potential Clinical Implications and Future Directions

ΔQRSA is a robust representation of the complex interaction between electrical substrate and CRT. If QRSA calculation were added to commercially available ECG analysis software, it would allow for many potentially useful applications, including assessment of CRT candidacy prior to device implantation, optimization of LV lead targeting, and risk

prediction and ECG based device optimization after CRT implantation. Future research is required to determine if ΔQRSA guided LV lead implantation and CRT optimization can improve reverse remodeling and long term outcomes among CRT patients. Importantly, continuous device based ΔQRSA measurements would allow for ongoing iterative optimization of single and multisite LV pacing during CRT therapy.

Limitations

This study has several important limitations including the retrospective study design and single center nature. There are several differences in baseline characteristics across ΔQRSA quartiles; as with any retrospective analysis, statistical adjustment may be incomplete and the possibility of residual confounding remains. ΔQRSA was calculated based on a single follow-up ECG which does not capture subsequent changes in LV activation due to device optimization; however, device optimization is rarely performed at our institution. Non-fatal endpoints (LVAD and transplant) were obtained from billing records and were not adjudicated based on blinded committee assessment and mode of death was not available. We were unable to assess the association between ΔQRSA and changes in NYHA class or quality of life as these scores were not routinely documented during routine clinical care. LV lead implantation in this study may not be optimized for non-LBBB patients; therefore it is possible that non-LBBB patients might demonstrate a greater decrease in QRSA with a different clinical implant strategy. QLV was infrequently measured during the study period and therefore we are unable to compare LV lead electrical delay and ΔQRSA. The study was conducted at a quaternary care center and therefore the results may not be generalizable to other patient care settings.

Conclusions

ΔQRSA is a robust representation of the complex interaction between a patient's electrical substrate and CRT pacing. Greater reductions in QRSA were associated with female sex, LBBB, longer QRS duration, non-ischemic cardiomyopathy and other characteristics associated with CRT response. CRT induced reductions in QRSA were associated with clinically meaningful differences in event free survival. ΔQRSA may be a novel target to guide lead implantation and device optimization.

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Figures

Figure 1. Bar graphs demonstrating pre-CRT QRS area (blue) and post-CRT QRS area (orange) overall and by ΔQRSA quartiles. The number over each pair of bars represents the average change in QRSA as calculated by subtracting the post-CRT QRSA from the pre-CRT QRSA and therefore a reduction in QRSA is indicated by a negative value.

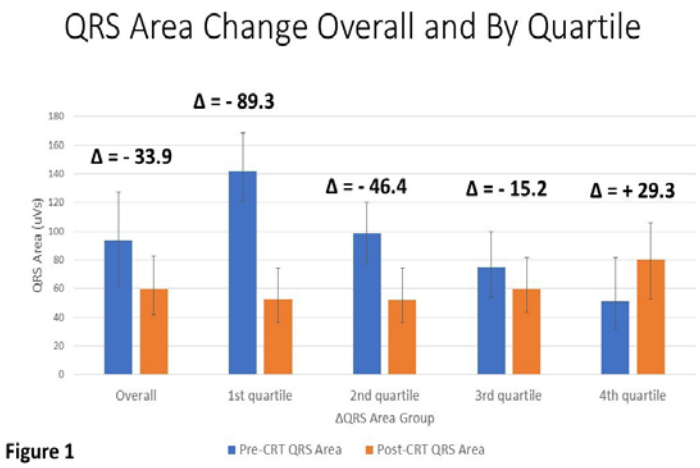

Figure 1

Figure 2. Kaplan Meier curve depicting the relationship between ΔQRSA quartile and incidence of LVAD, transplant, or death. Q1 had the greatest average reduction in QRSA and Q4 had an average increase in QRSA.

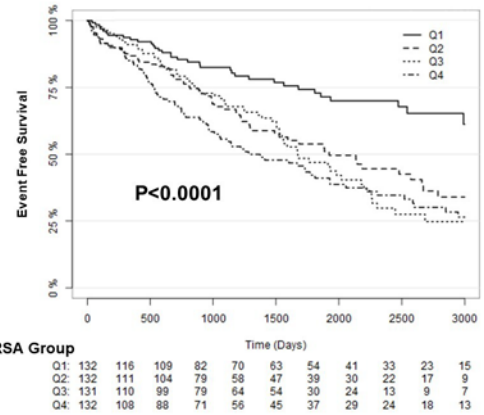

Figure 2

Figure 3. Forest plot depicting the adjusted association between ΔQRSA quartile and time until LVAD, transplant or death using an adjusted Cox proportional hazard model with Q4 as the reference. Adjusted for age, sex, atrial fibrillation or flutter, ischemic heart disease, ejection fraction, QRS morphology, beta blocker use, ACEi or ARB use, diabetes, NYHA class, and reduced eGFR, defined as <60 mL/min/1.73m^2.

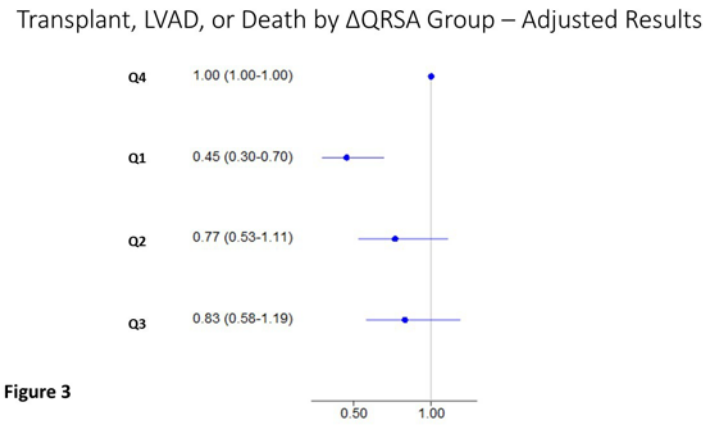

Figure 3

Figure 4. Adjusted spline function depicting the relationship between ΔQRSA across the continuous range and risk for LVAD, transplant, or death. Adjusted for age, sex, atrial fibrillation or flutter, ischemic heart disease, ejection fraction, QRS morphology, beta blocker use, ACEi or ARB use, diabetes, NYHA class, and reduced eGFR, defined as <60 mL/min/1.73m^2.

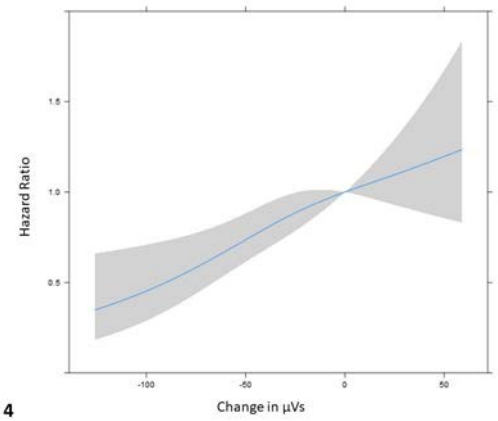

Figure 4

Figure 5. Forest plot depicting the adjusted association between ΔQRSA quartile and time until LVAD, transplant or death using an adjusted Cox proportional hazard model in the LBBB only cohort (n=338) with Q4 as the reference. Adjusted for age, sex, atrial fibrillation or flutter, ischemic heart disease, ejection fraction, QRS morphology, beta blocker use, ACEi or ARB use, diabetes, NYHA class, and reduced eGFR, defined as <60 mL/min/1.73m^2.

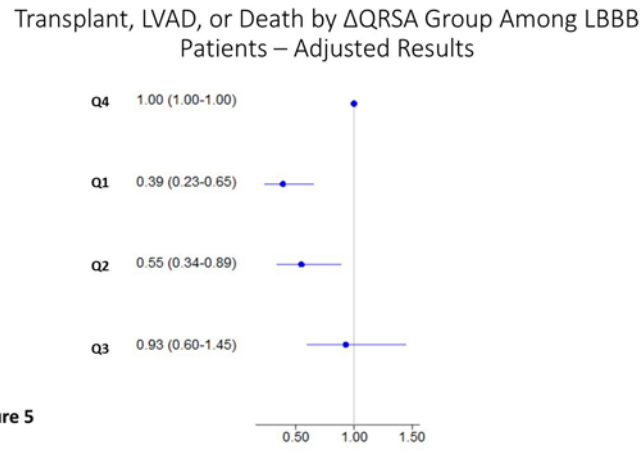

Figure 5

Tables

Table 1. Baseline clinical characteristics of the overall population after stratification by ΔQRSA

Variable	Total (n=527)	Q1 (n=132)	Q2 (n=132)	Q3 (n=131)	Q4 (n=132)	p-value
Age median [iqr]	67.7 [57.6, 75.2]	68.5 [55.8, 76.7]	67.4 [57.5, 73.3]	66.7 [59.4, 75.2]	68.0 [58.8, 75.2]	0.93
Female	161 (30.6)	52 (39.4)	48 (36.4)	24 (18.3)	37 (28.0)	<0.001
Race						
Black	104 (19.7)	31 (23.5)	28 (21.2)	26 (19.8)	19 (14.4)	
White	292 (55.4)	71 (53.8)	76 (57.6)	75 (57.3)	70 (53.0)	
Missing	113 (21.4)	25 (18.9)	22 (16.7)	25 (19.1)	41 (31.1)	
Other	18 (3.4)	5 (3.8)	6 (4.5)	5 (3.8)	2 (1.5)	0.15
Hispanic Ethnicity	8 (1.5)	3 (2.3)	2 (1.5)	0 (0.0)	3 (2.3)	0.39
Ejection Fraction	25.0 [20.0, 30.0]	25.0 [19.2, 30.0]	25.0 [20.0, 30.0]	25.0 [20.0, 30.0]	20.0 [15.0,30.0]	0.22
Ischemic Cardiomyopathy	285 (54.1)	56 (42.4)	69 (52.3)	77 (58.8)	83 (62.9)	0.005
Prior PCI	126 (24.0)	23 (17.4)	33 (25.0)	38 (29.0)	32 (24.6)	0.17

CABG	167 (31.7)	30 (22.7)	39 (29.5)	47 (35.9)	51 (38.9)	0.024
NYHA Class						
I	16 (3.0)	4 (3.0)	5 (3.8)	6 (4.6)	1 (0.8)	
II	64 (12.1)	19 (14.4)	18 (13.6)	15 (11.5)	12 (9.1)	
III	428 (81.2)	104 (78.8)	105 (79.5)	108 (82.4)	111 (84.1)	
IV	19 (3.6)	5 (3.8)	4 (3.0)	2 (1.5)	8 (6.1)	0.38
eGFR	60.0 [42.5, 76.0]	65.5 [49.8, 81.0]	56.5 [37.0,77.0]	60.0 [39.5, 79.0]	55.5 [42.0,69.2]	0.008
Dialysis	14 (2.7)	2 (1.5)	4 (3.0)	4 (3.1)	4 (3.0)	0.83
Primary prevention ICD	461 (87.5)	120 (90.9)	114 (86.4)	115 (87.8)	112 (84.8)	0.49
Prior ICD	108 (20.5)	16 (12.1)	28 (21.2)	36 (27.5)	28 (21.2)	0.021
Diabetes	202 (38.3)	45 (34.1)	51 (38.6)	49 (37.4)	57 (43.2)	0.50
Hypertension	377 (71.5)	90 (68.2)	90 (68.2)	98 (74.8)	99 (75.0)	0.40
Atrial Fibrillation or Flutter	180 (34.2)	33 (25.0)	41 (31.1)	50 (38.2)	56 (42.4)	0.015

Chronic Lung Disease	117 (22.2)	17 (12.9)	31 (23.5)	35 (26.7)	34 (25.8)	0.026
Cerebrovascular Disease	72 (13.7)	14 (10.6)	16 (12.1)	22 (16.8)	20 (15.3)	0.44
Amiodarone	92 (17.5)	11 (8.3)	27 (20.5)	23 (17.6)	31 (23.5)	0.008
Beta Blocker	468 (88.8)	122 (92.4)	118 (89.4)	112 (85.5)	116 (87.9)	0.34
ACE/ARB	410 (77.8)	113 (85.6)	99 (75.0)	101 (77.1)	97 (73.5)	0.08
Digoxin	87 (16.5)	16 (12.1)	18 (13.6)	25 (19.1)	28 (21.2)	0.15
Diuretic	449 (85.2)	111 (84.1)	109 (82.6)	112 (85.5)	117 (88.6)	0.55

Table 2. Baseline electrocardiographic characteristics of the overall population and after stratification by ΔQRSA

	Total (n=527)	Q1 (n=132)	Q2 (n=132)	Q3 (n=131)	Q4 (n=132)	P-value
QRS Morphology						
Strict LBBB	266 (50.5)	93 (70.5)	70 (53.0)	63 (48.1)	40 (30.3)	

Non-strict LBBB	72 (13.7)	2 (1.5)	15 (11.4)	30 (22.9)	25 (18.9)	
other	4 (0.8)	0 (0.0)	1 (0.8)	2 (1.5)	1 (0.8)	
RBBB	20 (3.8)	0 (0.0)	4 (3.0)	5 (3.8)	11 (8.3)	
RBBB + LAFB	41 (7.8)	1 (0.8)	7 (5.3)	6 (4.6)	27 (20.5)	
RBBB + LPFB	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.3)	
RV paced	91 (17.3)	35 (26.5)	32 (24.2)	16 (12.2)	8 (6.1)	
IVCD	30 (5.7)	1 (0.8)	3 (2.3)	9 (6.9)	17 (12.9)	<0.001
Baseline Rhythm						
Normal sinus rhythm	285 (54.1)	95 (72.0)	73 (55.3)	66 (50.4)	51 (38.6)	
Atrial paced	41 (7.8)	13 (9.8)	10 (7.6)	10 (7.6)	8 (6.1)	
Atrial fibrillation	75 (14.2)	10 (7.6)	16 (12.1)	21 (16.0)	28 (21.2)	
Atrial flutter	11 (2.1)	4 (3.0)	3 (2.3)	3 (2.3)	1 (0.8)	
1st degree AV block	89 (16.9)	7 (5.3)	23 (17.4)	23 (17.6)	36 (27.3)	
2nd degree AV block, Type I	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	

2nd degree AV block, Type II	3 (0.6)	0 (0.0)	0 (0.0)	2 (1.5)	1 (0.8)	
3rd degree AV block	12 (2.3)	1 (0.8)	4 (3.0)	3 (2.3)	4 (3.0)	
Other	8 (1.5)	2 (1.5)	3 (2.3)	2 (1.5)	1 (0.8)	<0.001
Atrial Rate	75.0 [66.0, 85.0]	75.0 [68.2, 85.0]	75.0 [66.0, 84.5]	73.0 [61.0, 86.0]	75.0 [65.0, 85.0]	0.75
missing	8	2	1	2	3	
PR Interval	182.0 [162.0, 206.0]	172.0 [154.0, 190.0]	184.0 [162.0, 206.0]	186.0 [168.0, 206.0]	194.0 [173.0, 220.0]	<0.001
missing	122	19	30	32	41	
QRS Duration	160.0 [144.0, 180.0]	174.0 [157.5, 188.5]	166.0 [152.0, 181.5]	152.0 [141.0, 174.0]	142.0 [132.0, 160.5]	<0.001
QT Interval	458.0 [426.0, 488.0]	465.0 [440.0, 490.5]	463.0 [425.5, 490.0]	452.0 [418.0, 492.0]	451.0 [418.5, 476.5]	0.29
QT Corrected	505.0 [475.0, 532.0]	517.0 [495.0, 547.2]	507.5 [480.8, 535.2]	492.0 [465.0, 523.0]	492.5 [470.0, 527.2]	<0.001
QRS Area	93.6 [61.3, 127.3]	141.8 [121.2, 168.7]	98.4 [77.5, 120.1]	75.2 [53.8, 99.6]	51.2 [32.7, 81.7]	<0.001

Table 3. CRT delivery in the overall population and after stratification by ΔQRSA

Variable	Total (n=527)	Q1 (n=132)	Q2 (n=132)	Q3 (n=131)	Q4 (n=132)	p-value
PAVD	130.0 [130.0, 170.0]	140.0 [130.0, 170.0]	135.0 [130.0, 170.0]	130.0 [130.0, 150.0]	130.0 [130.0, 170.0]	0.62095

NA	100	20	26	22	32	
SAVD	100.0 [100.0, 120.0]	100.0 [100.0, 120.0]	100.0 [100.0, 120.0]	100.0 [100.0, 120.0]	100.0 [100.0, 120.0]	0.77615
NA	123	26	32	30	35	
VV Pre-excitation						
RV, ≥40 ms	5 (0.9)	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.5)	
RV, 30 ms	3 (0.6)	1 (0.8)	0 (0.0)	1 (0.8)	1 (0.8)	
RV, 20 ms	9 (1.7)	2 (1.5)	1 (0.8)	2 (1.5)	4 (3.0)	
RV, 10 ms	7 (1.3)	0 (0.0)	6 (4.5)	1 (0.8)	0 (0.0)	
LV, 0 ms	221 (41.9)	59 (44.7)	53 (40.2)	55 (42.0)	54 (40.9)	
LV, 10 ms	14 (2.7)	1 (0.8)	2 (1.5)	6 (4.6)	5 (3.8)	
LV, 20 ms	37 (7.0)	10 (7.6)	12 (9.1)	7 (5.3)	8 (6.1)	
LV, 30 ms	20 (3.8)	10 (7.6)	5 (3.8)	3 (2.3)	2 (1.5)	
LV, ≥40 ms	44 (8.3)	13 (9.8)	10 (7.6)	13 (9.9)	8 (6.1)	
NA	167 (31.7)	35 (26.5)	42 (31.8)	42 (32.1)	48 (36.4)	0.11741
Adaptive CRT	57 (10.8)	22 (16.7)	13 (9.8)	13 (9.9)	9 (6.8)	0.06855
Quadripolar leads	79 (15.0)	28 (21.2)	17 (12.9)	17 (13.0)	17 (12.9)	0.14788

LV = left ventricle, NA = not available, PAVD = paced atrioventricular delay, RV = right ventricle, SAVD = sensed atrioventricular delay, VV = ventriculoventricular

Table 4. Association between ΔQRSA and outcomes among key patient subgroups

	Hazard Ratio (for each 1μVs decrease in QRSA)	P-value
Age (median 67.73 yrs)		
≤median (n=263)	0.993	0.001
>median (n=264)	0.992	<0.0001
Sex		
Male (n=366)	0.995	0.003
Female (n=161)	0.987	<0.0001
Ejection Fraction		
<20 (n=123)	0.998	0.359
≥20 (n=404)	0.990	<0.0001
QRS morphology		
LBBB (n=338)	0.990	<0.0001

RV paced (n=91)	0.994	0.112
Non-LBBB (n=98)	0.999	0.835
PR interval		
≥200 (n=129)	0.995	0.075
<200 (n=276)	0.994	0.002
QRSd		
≥150 (n=349)	0.994	0.0008
<150 (n=178)	0.991	0.0007
Baseline QRS Area (median 93.57 µVs)		
<median (n=263)	0.998	0.491
≥median (n=264)	0.995	0.029
Atrial fibrillation or flutter		
Yes (n=180)	0.996	0.052
No (n=347)	0.992	<0.0001
Coronary Artery Disease		

Yes (n=285)	0.995	0.008
No (n=242)	0.991	0.0001
CRT implantation Year		
2006-2010 (n=273)	0.993	<0.0001
2011-2015 (n=254)	0.992	0.002